Medical Progress

Prostaglandins, Thromboxanes and Leukotrienes in Clinical Medicine

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Although prostaglandin research began about 50 years ago, many of the most important advances in understanding the biochemistry, physiology and pharmacology have taken place within the past five to ten years. There is great potential for the extension of this research to the clinical practice of medicine. At this time, the most common interaction that clinicians have with the prostaglandin field is in administering nonsteroidal anti-inflammatory drugs, which function by inhibiting prostaglandins. The uses of these drugs include treating not only inflammation, but also dysmenorrhea, some renal diseases, thrombotic diseases and some metabolic disorders. Prostaglandin analogs, with their potent effects on uterine contraction, are in common use in obstetrics. Other analogs with gastric and duodenal cytoprotective effects are useful in treating peptic ulcer disease. Future benefits from prostaglandin and leukotriene research may include new therapy for inflammatory and hypersensitivity diseases such as asthma, inflammatory bowel disease and dermatitis.

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In this review we emphasize those areas of prostaglandin, thromboxane and leukotriene (collectively called "eicosanoids") biochemistry and physiology that interact with the contemporary practice of medicine. Additional emphasis will include discussions of assay methods, inhibitors and pharmacology to assist readers in interpreting the increasing number of publications that cover these areas. Eicosanoid research has made important contributions to several subspecialties, including cardiovascular and thrombotic disease, immunity and inflammation, reproduction, nephrology, pulmonary disease, gastroenterology and metabolic disorders. These areas will be discussed in more detail.

History and Introduction

The history of prostaglandins began in the 1930s with the observation by two New York gynecologists, Kurzrok and Lieb, that human semen caused contractions and relaxation of human myometrium.[1] These observations were soon confirmed by Goldblatt in England[2] and by von Euler in Sweden.[3] In 1935 von Euler purified the active compounds by acid lipid extraction of sheep vesicular glands and coined the term "prostaglandin" in the belief that the prostate was the source.[4] At about the same time, the history of leukotrienes began with the finding by Feldberg, Kellaway and Trethewie of a factor from dog lung exposed to cobra venom and a similar factor from sensitized guinea pig lung that caused a slow, prolonged contraction of the guinea pig jejunum.[5,6] These factors were called slow-reacting substance of anaphylaxis (SRS-A) and later identified as a possible mediator of asthma and other hypersensitivity reactions. There was then a delay in progress until the 1960s when a series of major advances began in Sweden by Bergström and colleagues, including Samuelsson, and in The Netherlands by Van Dorp. Prostaglandins were identified as a group of compounds rather than a single substance, and arachidonic acid was identified as their precursor.[7,8] Isolation of large amounts of natural prostaglandins from the Caribbean coral *Plexaura homomalla,* new methods of synthesis pioneered by Corey and others and extensive distribution of these products to investigators by the Upjohn Company and other pharmaceutical companies permitted intensive widespread study of these compounds. It was soon recognized that prostaglandins were produced by nearly all biologic tissue. Profound pharmacologic effects of these compounds were shown on smooth muscle contraction, cell secretions and platelet aggregation, which fostered the concept that prostaglandins functioned as local mediators of many biologic systems.

In 1971 the number of publications in this field began to

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ABBREVIATIONS USED IN TEXT

cyclic AMP = adenosine 3′:5′-cyclic phosphate
HETE = hydroxyeicosatetraenoic acid
HPETE = hydroperoxyeicosatetraenoic acid
LT = leukotriene
NSAID = nonsteroidal anti-inflammatory drug
PG = prostaglandin
SRS-A = slow-reacting substance of anaphylaxis
Tx = thromboxane

explode with the key discovery by Vane and colleagues in England that aspirin, indomethacin and other nonsteroidal anti-inflammatory drugs inhibited prostaglandin biosynthesis.[9] Over the past 12 years there have been more than 26,000 publications. Major highlights included the 1975 report by Hamberg, Svensson and Samuelsson identifying the potent platelet-aggregatory substance, thromboxane A_2,[10] and the 1976 identification by Moncada, Vane and co-workers of the antiaggregatory vasodilator, prostaglandin I_2.[11] During this time, parallel progress was made in studies of SRS-A including identification of arachidonic acid as the precursor.[12] In 1979 the Samuelsson laboratory announced the structures of the leukotrienes that make up the compounds of SRS-A.[13,14] New enzymatic pathways of arachidonic acid metabolism involving the lipoxygenase pathway were identified, as well as potent new biologic mediators of inflammation. In 1982 the Nobel prize for physiology and medicine was awarded to Sune Bergström, Bengt Samuelsson and John Vane for their major contributions to this field. The field continues to expand with an escalating number of publications on new metabolites of arachidonic acid, new inhibitors and a plethora of data on prostaglandin involvement in physiology.

Biochemistry

Prostaglandins and thromboxanes are derived from 20-carbon fatty acids. In mammals, arachidonic acid is the major precursor of prostaglandins ("2" series prostaglandins) and is localized primarily in the membrane phospholipids. Dihomo-γ-linolenic acid is the precursor of the "1" series prostaglandins (present only in trace amounts), and eicosapentaenoic acid (predominant in fish oils) is converted to some extent to the "3" series prostaglandins (Figure 1). Extreme variations in dietary fat and eicosapentaenoic acid, such as that derived from the marine diet of Greenland Eskimos, can compete with the enzymes governing arachidonic acid metabolism and alter prostaglandin and thromboxane synthesis, resulting in biologic changes such as prolonged bleeding time.[15] In essential fatty acid deficiency, prostaglandin synthesis is diminished, which may account for some of the clinical manifestations such as dermopathy.

The cascade of prostaglandin synthesis begins with the release of arachidonic acid from phospholipids via activation of phospholipase (primarily phospholipase A_2). This rate-limiting step is initiated by hormonal, ischemic, neural, inflammatory or other stimuli varying from cell to cell. Once released, arachidonic acid is available for enzymatic oxidation into hydroperoxy and hydroxy derivatives. For example, the 12-lipoxygenase enzyme in platelets induces formation of the unstable 12-hydroperoxyeicosatetraenoic acid (12-HPETE), which is reduced by peroxidase to the stable 12-hydroxyeicosatetraenoic acid (12-HETE), with unclear bio-

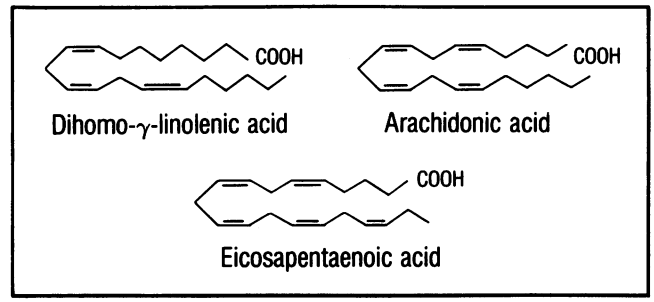

Figure 1.—Fatty acid precursors of eicosanoids.

logic activity. By a similar mechanism, 15-lipoxygenase in leukocytes forms 15-HPETE and 15-HETE, which may have some inflammatory activity. Two other enzymatic oxidation sites at carbon 11 and 5 are of more biologic importance, leading to formation of prostaglandins and leukotrienes, respectively. Aside from the biologic activity of the arachidonic acid metabolites, the oxidation-peroxidation reactions may have more direct biologic effects by forming oxygen radicals, which may induce tissue injury and carcinogenesis.[16,17]

Oxidation in the microsomes of most mammalian cells by the cyclooxygenase enzyme (originally called prostaglandin synthetase) at C 11 induces formation of a cyclopentane ring and a cyclic endoperoxide (prostaglandin [PG] G_2) (Figure 2). PGG_2 is rapidly converted by peroxidase activity to PGH_2, the unstable common intermediate of prostaglandins and thromboxanes. Conversion of PGH_2 to thromboxanes or to various prostaglandins is effected by enzyme systems characteristic for each specific cell type. Several examples are listed. PGE_2 and $PGF_{2\alpha}$ are the classic prostaglandins present in many tissues, including the kidney and uterus, with diverse possible physiologic actions including smooth muscle contraction, pyretic reactions and inflammatory interactions. PGI_2 (prostacyclin) is particularly prominent in vascular endothelium and possesses both vasodilatory and antiaggregatory actions. PGD_2 is a major product of mast cells and brain tissue. Thromboxane A_2 production is most commonly associated with platelet aggregation and vasoconstriction (see reviews.)[18-20]

Leukotriene formation, which predominates in polynuclear leukocytes and some mononuclear cells, results from 5-lipoxygenase activity forming 5-HPETE and conversion to an epoxide moiety, the unstable common intermediate, leukotriene (LT) A_4. LTA_4 can then react with water to form the potent chemokinetic and chemotactic leukotriene, LTB_4. Alternatively, LTA_4 reacting with glutathione leads to the peptide derivatives, LTC_4, LTD_4 and LTE_4, which make up the potent inflammatory mediators collectively known as SRS-A (see reviews.)[12,21-24] Recently, new compounds and pathways have been proposed, such as metabolites of 15-lipoxygenase, called lipoxins that may also have inflammatory functions.[25]

Eicosanoid Inhibitors

By far the most common interaction that clinicians have with the field of prostaglandins is the therapeutic use of nonsteroidal anti-inflammatory drugs (NSAIDs) and of corticosteroids for inflammatory conditions. The use of anti-inflammatory agents, however, certainly preceded prostaglandin research (willow bark has been used for centuries,

for instance, and acetylsalicylic acid has been commercially available since about 1900), and it is not established that all the effects of these drugs can be explained by their inhibiting the cyclooxygenase enzyme. A detailed review of NSAID pharmacology and clinical experience exceeds the scope of this summary, and excellent reviews are available.[26-32] Instead, in this summary we will briefly consider the modes of action of these agents, the prospect for more specific inhibitors and the relevance of the effects of these agents to our understanding of prostaglandin physiology.

In general, NSAIDs function by inhibiting the cyclooxygenase enzyme, thereby diminishing the conversion of arachidonic acid to PGH_2 and to other prostaglandins and thromboxanes.[9,13] The anti-inflammatory, analgesic and antipyretic actions of aspirinlike drugs are attributed to inhibition of prostaglandins, particularly PGE_2. Other anti-inflammatory drugs such as colchicine and gold do not inhibit prostaglandin. The NSAID effects on cyclooxygenase include diminished peroxidase activity and reduced generation of oxygen radicals, which may also reduce tissue damage and possibly reduce the formation of carcinogens. The anti-inflammatory potency of NSAIDs generally parallels the prostaglandin-inhibiting potency, although there is some variation in different tissues. For example, compared with newer NSAIDs, aspirin is a relatively weak prostaglandin inhibitor, but it causes a more prolonged inhibition of platelet thromboxane because the irreversibly acetylated cyclooxygenase enzyme cannot be regenerated in the life span of these cells. Acetaminophen is a poor cyclooxygenase inhibitor in most in vitro systems, but there is evidence that it may be effective in brain tissue, explaining its antipyretic and analgesic effects without peripheral anti-inflammatory effects.[32] Compared with indomethacin and ibuprofen, the new NSAID sulindac is less likely to cause acute renal impairment in patients with chronic glomerulonephritis or in those with cirrhosis and ascites[33,34]; however, it is not clear if this apparent renal sparing of sulindac is the result of rapid inactivation of the drug by the kidney or of overall weaker cyclooxygenase activity. Sodium salicylate reduces prostaglandin synthesis in sites of inflammation and in the pancreatic islet without inhibiting gastric mucosal or platelet prostaglandins.[35]

Finally, caution is urged in extrapolating specific physiologic functions of prostaglandins from the effects of NSAIDs. The NSAIDs are considered "nonspecific" because they inhibit all of the cyclooxygenase products and also because they act on multiple organ systems. The observed effects may be the culmination of effects on several biologic systems. These agents also have nonprostaglandin effects. For example, indo-

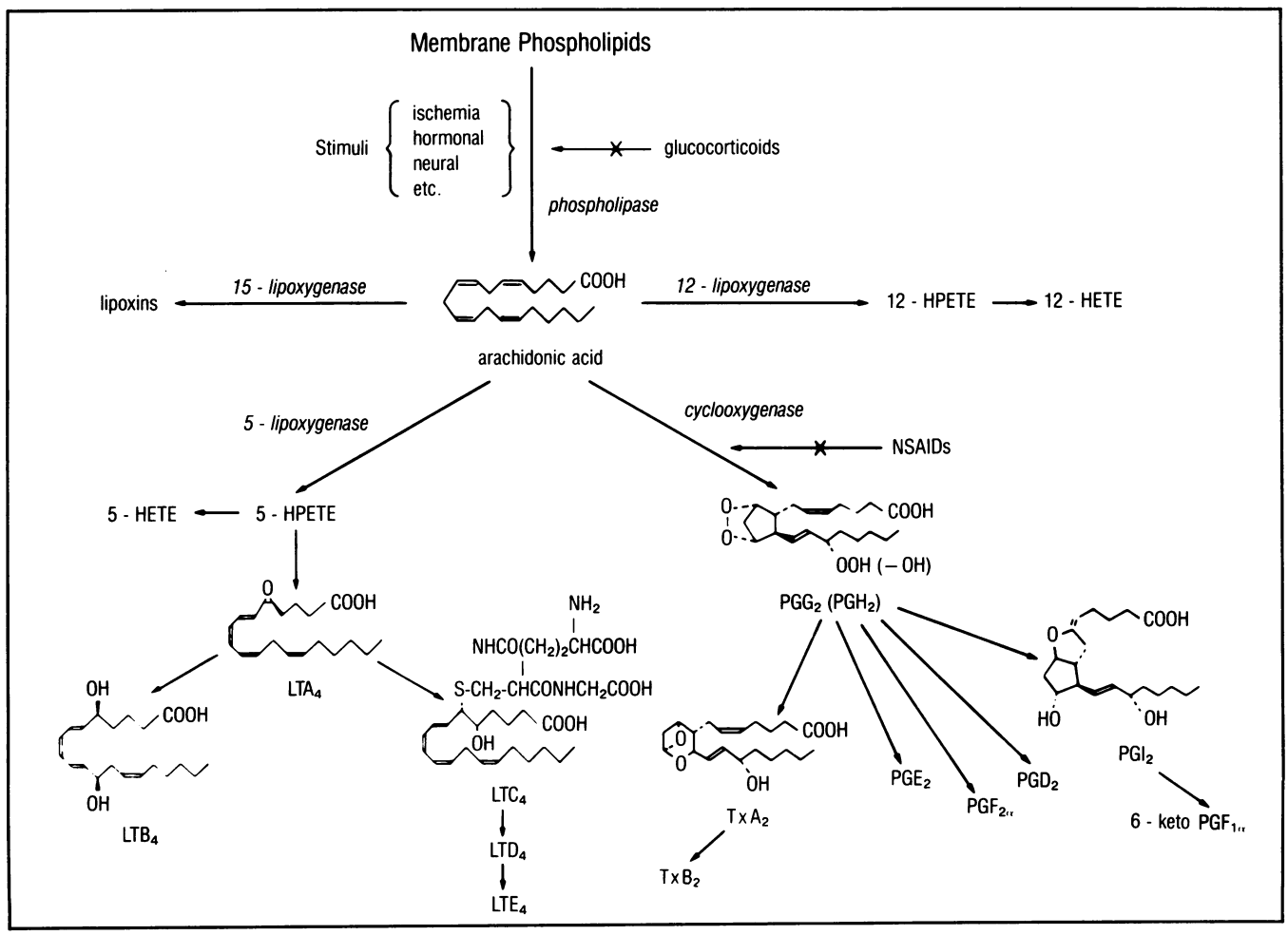

Figure 2.—Eicosanoid biochemical pathways. HETE = hydroxyeicosatetraenoic acid; HPETE = hydroperoxyeicosatetraenoic acid; LT (A_4, B_4, C_4, D_4, E_4) = leukotriene; NSAIDs = nonsteroidal anti-inflammatory drugs; PG (D_2, E_2, $F_{1\alpha}$, $F_{2\alpha}$, G_2, H_2, I_2) = prostaglandin; Tx(A_2, B_2) = thromboxane

methacin in high concentrations affects protein kinase, calcium flux and other enzymes.[29] In addition, at least some of the NSAIDs also block arachidonic acid metabolism by the 15-lipoxygenase enzyme, perhaps contributing to the anti-inflammatory effects.[30]

Inhibitors of specific enzyme pathways distal to the cyclooxygenase enzyme have recently been developed with possible clinical implications. The first to undergo clinical trials have been imidazole and pyridine derivatives, which selectively block thromboxane synthetase without reducing other cyclooxygenase products.[36,37] The premise is that these drugs will have antithrombotic action because they block platelet thromboxane without reducing blood vessel synthesis of prostacyclin. Early clinical trials of patients with thrombotic and vasospastic disease have suggested some benefit but no clear advantage over aspirin. Clinical application may have more promise in other disease states such as glomerulonephritis.[38]

Pharmacologic administration of glucocorticoids causes many effects unrelated to arachidonic acid metabolism. At least in some biologic systems, these steroids inhibit the release of arachidonic acid from membrane phospholipids.[39] This effect involves synthesis of a glycoprotein that inhibits phospholipase A_2 activity.[40,41] The new term "lipocortins" best describes this family of compounds.[42] In susceptible tissue, all arachidonic acid metabolites are inhibited, including cyclooxygenase and lipoxygenase systems. The anticipated reduction in leukotriene synthesis is the popular explanation for some of the glucocorticoid efficacy in cases of hypersensitivity reaction such as asthma and in inflammatory states. Fostered by these studies and the increasing amount of data on the potent effects of leukotrienes, there is currently an intense effort to develop specific leukotriene inhibitors for clinical uses that may include patients with asthma, inflammatory arthritis, dermatitis and inflammatory bowel disease.[43]

Methodologic Constraints

It has been the unfortunate recurring history of prostaglandin assays in clinical research that the early studies of each eicosanoid report biologic levels that greatly exceed those subsequently determined with better methods. The physiologic roles equated with the early measurements are then subsequently disproved. For example, many early studies of plasma and serum PGE_1, PGE_2, PGA_1 and PGA_2 reported normal values ranging from several hundred picograms to several hundred nanograms per milliliter. Theories on the pathogenesis of blood pressure regulation, sodium balance and diarrheal states were widely promulgated based on these reports. Later studies using mass spectrometry confirmed that PGA_1 and PGA_2 did not exist in detectable amounts in human circulation and that PGE_2 plasma levels were less than 30 pg per ml. Similar misadventures have occurred with reports of circulating levels of prostacyclin (PGI_2), thromboxane B_2, $PGF_{2\alpha}$ and some prostaglandin metabolites (see reviews).[19,44,45] It is now clear that none of these compounds are present in sufficient concentration to act as circulating hormones; instead, eicosanoids function primarily as local mediators. The methodologic problems are caused by several factors, which include poor antiserum specificity in early radioimmunoassays, the myriad of unidentified prostaglandin metabolites that may cross-react in these assays, poor specificity and sensitivity of bioassays, the pronounced potential for artifactual generation of eicosanoids during sample collection—such as from platelet release and vessel wall trauma during blood sampling—the short biologic and chemical half-life of many eicosanoids and unidentified interfering substances in early mass spectrometry. It behooves the reader of prostaglandin research to be cautious of all reports of circulating blood and urine levels unless extensive validating studies (particularly comparison with mass spectrometry) have been presented. Measurements of tissue concentration of eicosanoids are suspect because these compounds are generally not stored and because they are readily produced by tissue trauma, such as by biopsy. One technique to avoid these problems is to measure stable metabolites. For example, urinary excretion of 2,3-dinor-$PGF_{1\alpha}$ and 2,3-dinor-thromboxane B_2 appear to quantitatively reflect systemic production of prostacyclin and thromboxane, respectively,[46] and plasma assay of a tetranor metabolite of $PGF_{2\alpha}$, which has a long half-life in circulation, accurately reflects systemic production of $PGF_{2\alpha}$.[47]

Cardiovascular and Thrombotic Diseases

The role of prostaglandins in controlling blood pressure has been a topic of dispute for almost 20 years since the isolation of prostaglandin A_2 from kidney medulla and the early reports claiming that circulating levels of PGA_2 were of sufficient concentration to affect blood pressure.[48-50] Later studies showed that PGA_2 was not present in the circulation.[51] Similarly, other vasodepressor prostaglandins such as PGI_2 exist in blood in concentrations too low to have circulating hormonal effects.[52] Nevertheless, it is likely that local vascular production of vasodilatory prostaglandins and possibly vasoconstrictor thromboxanes do function to modulate local vascular resistance, especially in response to vasopressor hormones and to volume. Thus, administering NSAIDs may increase blood pressure (aside from the sodium-retaining effects) in a few patients such as those with mineralocorticoid-induced hypertension,[53] and NSAIDs may blunt the effects of antihypertensive drugs.[54] The hemodynamic effects of these agents are particularly evident in patients with congestive heart failure.[55]

A more contemporary issue is the possible role of prostacyclin (PGI_2) and thromboxane (Tx) A_2 in regulating platelet aggregation in patients with thrombotic and atherosclerotic disease. Thromboxane A_2, a major arachidonic acid product of platelets, is a potent vasoconstrictor (similar in potency to angiotensin II), platelet-aggregatory stimulus (independent of adenosine diphosphate and thrombin) and bronchoconstrictor.[10] TxA_2 has a short half-life (30 seconds in aqueous media) and spontaneously converts to the inactive TxB_2. Following vascular wall trauma, collagen and other factors stimulate platelet aggregation and thromboxane release. Aspirin, other NSAIDs and selective thromboxane-synthesis inhibitors block thromboxane generation and prolong bleeding time in vivo and platelet aggregation in vitro.[9,56-58] Opposing effects result from PGI_2, the predominant arachidonic acid metabolite of intact vascular endothelium with vasodilatory and bronchodilatory properties.[11] PGI_2 inhibits platelet aggregation and prevents TxA_2 production via a platelet adenosine 3′:5′-cyclic phosphate (cyclic AMP)-mediated pathway.[57,59] Dipyridamole, an inhibitor of phosphodiesterase, also increases cyclic-AMP levels, inhibits platelet aggregation by cyclic

AMP of other mechanisms and potentiates the antiaggregatory effect of aspirin.[60] As with TxA_2, PGI_2, has a short half-life (about 1.5 minutes in aqueous solution), and it is converted to an inactive metabolite, 6-keto-prostaglandin $F_{1\alpha}$, but possibly also to an active metabolite, 6-keto-PGE_1, in some tissues. The general interpretation of these studies is that the intact endothelium prevents platelet adherence and aggregation via local generation of PGI_2 (plus several other antiplatelet factors). With disruption of the endothelium, initial platelet adherence occurs and platelet TxA_2 is then produced that causes local vasoconstriction and augments platelet aggregation at the injury site. Production of PGI_2 from normal endothelium adjacent to the injury site may be increased by the use of endoperoxide precursors (PGH_2) released during arachidonic acid metabolism from the platelets and taken up by the endothelium, thus preventing spread of platelet aggregation to normal endothelium (Figure 3).[57,59-61]

One clinical implication of these opposing effects of TxA_2 and PGI_2 is the concept that an imbalance of these products may contribute to thrombotic, atherosclerotic and vasospastic disease.[62] This concept is supported by several in vitro studies showing increased thromboxane generation from disease states susceptible to atherosclerosis, such as hypercholesterolemia[63] and diabetes mellitus.[64] Conversely, high-density lipoproteins are associated with a reduced risk of cardiovascular disease and in vitro studies have shown an increased endothelial PGI_2 response to high-density lipoprotein.[65] In addition, smoking decreases the urinary excretion of a PGI_2 metabolite.[66] Although the theories of imbalances of arachidonic acid metabolites as a cause of atherosclerosis are intriguing, rigorous evidence of clinical relevance is still lacking. Indeed, recent data suggest that systemic PGI_2 production may actually be increased rather than decreased in patients with atherosclerosis.[67] Based on this imbalance theory, therapeutic strategies to prevent cardiovascular disease that attempt to selectively reduce TxA_2 without impairing PGI_2 have been proposed, including administering very low doses of aspirin (to block platelet but not vascular cyclooxygenase), administering selective inhibitors of thromboxane synthetase and prescribing diets rich in eicosapentaenoic acid (fish oils).[68] Although controversy persists, increasing data suggest that administering aspirin (with or without dipyridamole) is of benefit in reducing the risk of myocardial infarction in some patients and in reducing reocclusion of saphenous vein coronary artery bypass grafts.[69-71] These data provide clinical support at least for the importance of platelet aggregation and thromboxane in these diseases. A role for PGI_2 is likely, but not proved.[72]

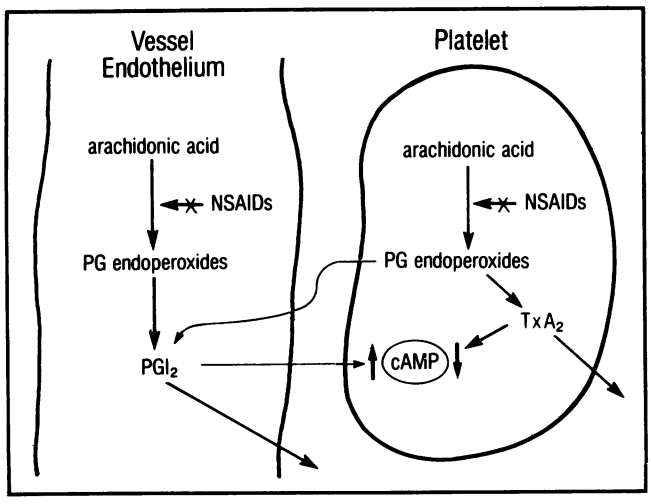

Figure 3.—Thromboxane (Tx) and prostacyclin (prostaglandin [PG]I_2) interactions from platelets and blood vessel endothelium. cAMP = cyclic AMP (adenosine 3′:5′-cyclic phosphate), NSAIDs = nonsteroidal anti-inflammatory drugs

Another exciting extension of prostaglandin research to cardiovascular disease is the pharmacologic administration of prostacyclin (PGI_2) or a stable analog for its platelet antiaggregatory and vasodilatory effects.[73] Prostacyclin has been substituted for heparin during extracorporeal circulation such as hemodialysis, cardiopulmonary bypass and charcoal perfusion.[74-77] Compared with the effects of heparin therapy, thrombocytopenia is reduced or prevented, most platelet functions are maintained and blood loss may also be reduced. The use of prostacyclin has also been advocated for treating patients who have atherosclerotic obstruction of extremities, central retinal vein occlusion, angina pectoris or ischemic strokes based on the premise that atherosclerotic arteries have decreased prostacyclin production. Initial results of uncontrolled studies are promising.[78,79] Earlier studies using infusions of PGE_1 also claimed relief of pain and ulcer healing in patients with chronic ischemia of the legs.[80] Open trials of prostacyclin infusion in patients with the Raynaud's phenomenon have also suggested prolonged improvement.[81] Results of double-blind controlled trials have suggested that these infusions are not consistently beneficial[82-84] and such therapy will probably not become clinically useful.

Immune and Inflammatory Responses

Perhaps the areas with the most rapidly expanding knowledge about eicosanoid physiology are those of immunity and inflammation.[21-23,28,31,85-88] Increased production of arachidonic acid metabolites occurs at sites of inflammation,[85-89] arising from the injured tissue, from inflammatory cells and from noninflammatory cells that are apparently stimulated by other products of inflammation.[90,91] Oxygen free radicals are generated by both cyclooxygenase and lipoxygenase pathways, and these products likely contribute to tissue injury.[92] Several prostaglandins, especially PGE_2, PGI_2 and possibly PGD_2, contribute to inflammation by increasing the blood flow (erythema), by dilating vessels and increasing capillary permeability (edema) and by increasing pain sensitivity to other mediators such as to bradykinin and histamine. Prostaglandins also have pyretic effects under some conditions such as following release of leukocytic pyrogen and endotoxin.[93,94] It is unclear whether the cyclooxygenase products have chemotactic and chemokinetic properties: discrepant results have been reported in several studies. However, leukotriene B_4 is a very potent chemotactic factor for neutrophils, eosinophils and mononuclear cells.[31,95] Some mono-HETEs are less potent chemotactic agents. LTB_4 also activates neutrophils by causing degranulation and superoxide generation. LTC_4, LTD_4 and LTE_4 (SRS-A) have vasoconstrictor activity; they also contribute to edema by increasing capillary permeability. These SRS-A factors are from 100-fold to 10,000-fold more potent than histamine in constricting pulmonary airways. It is apparent that the anti-inflammatory effects of NSAIDs and of corticosteroids function in part by inhibiting the eicosanoid

actions cited above. It should be emphasized that eicosanoids act primarily as potentiators (or in some cases as modulators), rather than as initiators, of inflammation. In some inflammatory conditions the effects of certain eicosanoids may predominate, favoring the use of specific blockers of the arachidonic acid cascade. For example, lipoxygenase products may be particularly important in cases of psoriasis,[96,97] inflammatory bowel disease[98] and rheumatoid arthritis,[99] whereas PGD_2 predominates in mastocytosis.[100]

In contrast to the apparent proinflammatory actions, eicosanoids generally suppress immune functions.[87,88] In low concentrations, PGE_2 suppresses T-lymphocyte functions that include antigenic stimulation, lymphokine production, lymphocyte migration, mitogen responsiveness and clonal proliferation. These actions are mediated by enhanced generation of cyclic AMP. LTB_4 and 15-HPETE may have similar effects. NK-cell and monocyte cytolytic activity is inhibited by PGE_2 and by lipoxins, although lipoxins may act independently of cyclic AMP. Prostaglandins may also inhibit B-cell function, either directly or via actions on other immune cells. Macrophages and monocytes produce large amounts of PGE_2 in response to lymphokines and other stimuli that include zymosan, endotoxins, antigen-antibody complexes and immunoglobulin-G fragments. A popular theory is that antigens stimulate lymphocyte production of lymphokines, which activate macrophages to produce prostaglandins. These prostaglandins then function to inhibit the lymphocyte function.[101] In cases of Hodgkin's disease the defect in cellular immunity is due to a population of prostaglandin-producing suppressor cells.[102] Immunosuppressive activity from macrophages (presumably via prostaglandin production) may contribute to the anergy present in patients with chronic inflammatory diseases such as Q fever, coccidioidomycosis and tuberculosis.[103]

These pieces of information are consistent with the theory that eicosanoids function predominantly as potentiators of acute inflammation, actions that are inhibited by corticosteroids and by NSAIDs. In contrast, in some chronic disease states, eicosanoids function to depress cellular immunity and prostaglandin inhibitors may act to stimulate cellular immune function.

Reproduction

Another important impact of prostaglandin research on clinical medicine involves reproduction, including the extensive use of exogenous prostaglandins as pharmacologic agents.[104-107]

Seminal fluid contains the highest concentration of prostaglandins of all human tissue, more than 100,000-fold more concentrated than in circulating plasma.[108,109] This observation has led to speculation that seminal fluid prostaglandins are involved in the contractile response of the vas deferens and the uterus, although the precise function in fertility is not established. There is some evidence, however, of diminished seminal fluid prostaglandin concentration in some infertile men who have no other apparent abnormality.[110]

There is pronounced species variation in the physiologic functions and pharmacologic effects of prostaglandins in female reproductive organs. In rats and rabbits, but not in humans, prostaglandins are obligatory mediators of ovulation.[111,112] Gonadotropin-stimulated cyclic AMP in the granulosa cell induces prostaglandin synthesis.[107,113] Indomethacin prevents follicular rupture, and exogenous prostaglandins reverse this effect. In many species including sheep, cows, horses and pigs, prostaglandin production (possibly $PGF_{2\alpha}$ from the uterus) is the key factor causing luteolysis.[113-115] Prostaglandin administration has been used to synchronize the estrous cycle of cows and other animals to facilitate artificial insemination.[116] In humans, there is no strong evidence that prostaglandins or prostaglandin inhibitors have direct effects on ovulation or on maintaining the corpus luteum. There is substantial evidence, however, that increased production of endometrial prostaglandins contributes to the symptoms of dysmenorrhea, and NSAIDs are now widely prescribed for these symptoms.[117-119] Several clinical trials have confirmed the safety and efficacy of these drugs for such symptoms as uterine cramps, headache, nausea and diarrhea.[120] NSAIDs are also used to treat dysfunctional uterine bleeding, especially in association with intrauterine contraceptive devices.[121,122]

During pregnancy, the uterus is particularly sensitive to PGE_2, $PGF_{2\alpha}$ and their analogs. Endogenous prostaglandins may mediate uterine contractions in nonsurgical abortions,[123] and exogenous prostaglandins are widely used for terminating pregnancy, particularly in the second trimester.[104,105] Major complications of this treatment include bronchospasm, shock, seizures and cervicovaginal fistulas. Gastrointestinal symptoms are common. Prostaglandins are generally more effective, however, and are associated with less frequent serious side effects than hypertonic saline.[124] Side effects are also minimized with local administration (intrauterine or intravaginal instead of oral, intravenous or intramuscular) and with newer analogs.[125,126] Abnormal pregnancies, such as missed abortions and intrauterine fetal death, appear particularly sensitive to exogenous prostaglandins.[127]

Karim and co-workers in Singapore first reported the use of prostaglandins for inducing labor in 1968.[128] However, oxytocin generally remains the drug of choice.[104,107,129] NSAIDs may prolong gestation and delay the onset of labor. These drugs should not be used for treating cases of premature labor as they potentially affect fetal pulmonary circulation and hemostasis.[130] Endogenous prostaglandins may be involved in cervical ripening,[131] and exogenous prostaglandins have been used to hasten cervical ripening at term.[132] Prostaglandins may also be effective in controlling postpartum hemorrhage.

NSAIDs are an established therapy for closing a patent ductus arteriosus in premature newborns.[133,134] It is likely that prostaglandins (probably PGE_2 or PGI_2) function to maintain patency of the ductus during normal fetal life. These prostaglandins arise from ductal tissue or possibly from the lung. At birth, the ductus normally closes in response to increased oxygen tension, possibly related to a fall or a shift in prostaglandin synthesis.[135-137] Exogenous prostaglandins may be infused to prevent closure of the ductus arteriosus when it is critical to maintain fetal circulation, such as with congenital right ventricular outflow obstruction, transposition of the great arteries and with some anomalies of the aortic arch.[136]

Renal Function

There has been extensive research summarized by thorough reviews on the role of prostaglandins in renal physiology.[138-144] Prostaglandins have been implicated in the physio-

logic control of renal hemodynamics, renin release, sodium excretion and water transport. There are extensive data on possible functions of prostaglandins and thromboxanes in a number of renal diseases, including Bartter's syndrome, obstructive uropathy, functional renal impairment associated with liver disease, glomerulonephritis, acute and chronic renal failure and renal transplant rejection. In this review we will emphasize the clinical applications of these data, particularly the beneficial and adverse effects of NSAIDs.

Bartter's syndrome was the first renal disorder clearly recognized to involve augmented renal prostaglandin synthesis.[145-147] Increased renal synthesis of PGE_2 or PGI_2 from different regions of the kidney and peripheral vasculature contribute to the hyperreninism, sodium depletion, polyuria, low blood pressure, resistance to the pressor effects of angiotensin and norepinephrine, increased urinary excretion of prostaglandins and possibly to the hypokalemia. Administering indomethacin and other NSAIDs greatly alleviates these abnormalities, and NSAIDs are now the standard treatment. However, chloride wasting is likely the primary abnormality of this disorder and prostaglandins are probably secondary mediators. Giving NSAIDs does not fully correct the hypokalemia.[148] In patients with the more common disorders involving volume depletion or relative underperfusion of the kidneys, such as diuretic administration, surreptitious vomiting, congestive heart failure and cirrhosis with ascites, the increased prostaglandin excretion and prostaglandin-mediated hyperreninism are also reduced by NSAIDs.[143,144,149-153] Results of these clinical studies and of many animal and in vitro studies support the concept that prostaglandins (probably PGI_2 produced in the renal cortex) are involved in renin release, although prostaglandins are not obligatory intermediates, as profound stimuli arising from sodium depletion, β-adrenergic stimuli or hypotension causes renin release despite cyclooxygenase inhibition.[154-158] An additional clinical implication of these observations is that during renin determination for classification of hypertension or other conditions, NSAIDs will suppress renin activity and withdrawal of NSAIDs may cause a rebound elevation in renin.[159] Prolonged suppression of renin and the secondary suppression of aldosterone in some patients with mild chronic renal impairment may cause hyperkalemia and mimic the syndrome of hyporeninemic hypoaldosteronism.[160]

Synthesis of renal cortical vasodilatory prostaglandins is enhanced in patients with glomerulonephritis or underperfusion of the kidney, such as in those who have cirrhosis with ascites, heart failure or sodium depletion. These prostaglandins function to maintain renal perfusion, countering vasoconstrictor stimuli such as catecholamines and angiotensin. Administering NSAIDs to these susceptible patients unmasks the underlying renal vasoconstriction and results in an abrupt decrease in renal blood flow and glomerular filtration rate.* This situation is most dramatic in patients with cirrhosis and ascites in whom as little as 25 mg of indomethacin may cause anuria for several hours.[151-153] A diminished glomerular filtration rate may contribute to the apparent beneficial effects of NSAIDs to reduce proteinuria in patients with nephrotic syndrome, although a more direct prostaglandin effect on proteinuria may also be involved.[165]

*Reference numbers 143, 144, 151-153, 161-164.

The role of renal prostaglandins in sodium excretion is incompletely understood. Clearly, various NSAIDs cause sodium retention—generally about 150 mEq over several days in healthy subjects with greater retention in patients with various disease states.[166] The intrarenal site of action for this effect may involve active chloride transport in the ascending limb of Henle, sodium absorption in the cortical collecting tubule or reduced glomerular filtration.[138-141,167,168] The involvement of prostaglandins in sodium excretion is most pronounced during diuretic administration. NSAIDs including aspirin and sulindac greatly impair the natriuretic response to furosemide, spironolactone and other diuretics.[34,169-171] There is increasing evidence that prostaglandins are also involved in water excretion. A series of studies by Orloff and others suggested that prostaglandins produced in the collecting tubule may function as a negative feedback inhibitor on antidiuretic hormone-stimulated water reabsorption.[172-174] Although the interactions of antidiuretic hormone, cyclic AMP and prostaglandins are complex and not fully understood,[175] it is clear that NSAIDs contribute to water retention in humans and may contribute to dilutional hyponatremia. Alternatively, these drugs may be useful in reducing water loss in patients with central diabetes insipidus.[138,140] NSAIDs also decrease water loss in patients with nephrogenic diabetes insipidus, indicating that the drugs also act independently of antidiuretic hormone, apparently by altering the medullary or glomerular blood flow.[176]

A series of animal studies by Morrison, Needleman and associates have shown that a ureteral obstructed kidney produces large amounts of thromboxane A_2, which may increase renal vascular resistance and diminish renal blood flow.[177,178] A similar situation occurs after partial obstruction of the renal vein.[179] In these models, fibroblast and mononuclear cell infiltration is the source of the augmented thromboxanes.[180] Renal thromboxane production is also increased in experimental glomerulonephritis.[181] The role of vasoconstrictor thromboxane in human renal function is less clear. Thromboxanes do not regulate renal blood flow in normal persons.[182] Urinary TxB_2 is greatly increased in patients with the hepatorenal syndrome,[183] but thromboxanes are probably not the cause of the renal vasoconstriction.[184] In patients with renal transplant rejection, urinary TxB_2 is also increased and serves as an early indication of rejection.[185] In this disorder it is likely that thromboxanes from infiltrating cells contribute to the rejection process. Platelet generation of thromboxanes or prostaglandins may also have deleterious long-term effects on the progression of membranoproliferative glomerulonephritis in humans.[38]

Pulmonary Physiology and Diseases

In studies using pharmacologic amounts of eicosanoids in isolated tissues, animals and humans, possible functions of these chemicals have been suggested in regulating lung vascular and bronchial smooth muscle tone and in mucus secretion.[186,187] Although there are species and preparation differences, pulmonary vascular constriction is caused by PGE_2 (opposite to its peripheral vasodilatory effect), PGD_2 and $PGF_{2\alpha}$.[186-189] PGE_1 is a vasodilator, and administering a PGE_1 analog to patients with chronic lung disease is effective in lowering pulmonary vascular resistance but does not immediately improve pulmonary function.[190] PGI_2 is also a potent

vasodilator and weak bronchodilator, and infusions of PGI_2 have been administered for treating pulmonary hypertension.[191]

$PGF_{2\alpha}$, TxA_2 and PGD_2 are bronchoconstrictors, and the bronchoconstrictive effect of $PGF_{2\alpha}$ aerosol is greatly potentiated in patients with asthma.[187,192] In contrast, PGE_1 and PGE_2 are bronchodilators and block the effects of $PGF_{2\alpha}$.[193] As described above, leukotrienes C_4, D_4 and E_4 are extremely potent bronchoconstrictors, perhaps 1,000-fold more potent than histamine on bronchial tissue.[194-196] These leukotrienes also stimulate mucus secretion and increase vascular permeability.

These pharmacologic data are not synonymous with physiologic functions. However, there is strong evidence for eicosanoid activity in several types of pulmonary disease, particularly in patients with asthma.[197] SRS-A (now identified as peptide leukotrienes) has been implicated as a key mediator of allergic bronchospasm for decades.[198] These leukotrienes are synthesized in human lung tissue, especially from pulmonary mast cells.[199,200] Leukotriene generation is increased during an allergic challenge in patients with asthma in parallel with the onset of bronchoconstriction.[201] In contrast to their hypersensitive response to $PGF_{2\alpha}$, however, patients with asthma have the same degree of bronchoconstriction response to LTD_4 as do those who do not have asthma.[202] In guinea pigs, part of the leukotriene-induced bronchoconstriction is mediated by augmented TxA_2 release,[203] but in humans the leukotriene effect is independent of cyclooxygenase products.[204] About 15% of patients with asthma have an attack following ingestion of an NSAID, apparently related to cyclooxygenase inhibition[205] and possibly due to a shift in arachidonic acid metabolism from cyclooxygenase to lipoxygenase products. Corticosteroids are a well-established therapy for persistent asthma, and these drugs reduce lipoxygenase products, supporting the link between leukotrienes and asthma. Proof of this association and possible new therapeutic modalities must await development of specific leukotriene inhibitors.[43]

Eicosanoids have been implicated in several other types of acute pulmonary injury.[206,207] With massive pulmonary emboli, thromboxane release from activated platelets or lung parenchyma contributes to the hemodynamic alterations.[208] Assay of thromboxanes excreted in the urine may be a useful adjunct to diagnosing acute thromboembolic disease.[209] Thromboxanes and other cyclooxygenase products may also contribute to the pulmonary hypertension and respiratory distress that develops after trauma, fat emboli and possibly sepsis.[206,207,210,211] In studies of animals, cyclooxygenase and thromboxane inhibitors improve cardiopulmonary hemodynamics.[210-213] Infusions of PGI_2 or PGE_1 may also be useful by countering the effects of thromboxane, and clinical trials in humans are in progress.

Cyclooxygenase products are released into the circulation in large amounts during septic shock in animals and humans, and these products may also contribute to the systemic cardiovascular changes, including myocardial depression.[213-217] At least in some animal models of septic shock, pretreatment with thromboxane inhibitors improves survival.[214,216,217] The clinical usefulness of these agents for treating septic shock in humans has not been shown.

In inflammatory diseases of the lung, as with inflammation elsewhere, prostaglandins and leukotrienes are likely involved. During inflammatory insults, such as bleomycin administration and exposure to asbestos fibers, an interaction between alveolar macrophages and fibroblasts involving prostaglandin E_2 and interleukin 1 may lead to collagen production and pulmonary fibrosis.[218,219]

Gastrointestinal Physiology

Administering large amounts of prostaglandin E or F, such as for terminating a pregnancy, frequently causes diarrhea.[220,221] This phenomenon was initially attributed to direct stimulation of intestinal smooth muscle; it is now clear, however, that prostaglandins enhance intestinal fluid and electrolyte secretion and cause a secretory diarrhea.[222,223] Prostaglandins of the E and F type increase cyclic AMP in the small intestine and probably also in the colon, similar to the effects of cholera toxin.[224,228] Although still controversial, prostaglandins probably have only a minimal or secondary role in cholera toxin-induced diarrhea,[229] and prostaglandin inhibitors have not proved useful in treating human cholera infection. Endogenous prostaglandins may have a physiologic role in jejunal secretion in humans,[230] and augmented intestinal prostaglandin synthesis may contribute to the diarrhea associated with *Salmonella, Shigella* and *Escherichia coli* infections[231]; however, as in cholera infections, NSAIDs have not been clinically beneficial.

Prostaglandins have also been claimed to play a role in the diarrhea associated with a variety of noninfectious causes, including laxatives—such as bisacodyl, senna compounds, docusate sodium (dioctyl sodium sulfosuccinate)—thyrotoxicosis, hypergastrinemia, radiation-induced enteritis, irritable bowel syndrome and paraneoplastic syndromes.[224-226] It is difficult to interpret many of these early studies that suggested an association between prostaglandins and these clinical states. Some of the early prostaglandin assays of blood or intestinal contents were later shown to be problematic. The clinical response to NSAIDs often did not relate to increased basal prostaglandin levels. Studies done on animals were not always repeated in humans, and many publications were isolated case reports. In an excellent review, Metz, McRae and Robertson discuss the criteria to assess these publications.[232] Nevertheless, it is likely that overproduction of prostaglandins contributes to the diarrhea of a few patients with pancreatic tumors, medullary carcinoma of the thyroid and perhaps other conditions,[232,233] and a therapeutic trial of NSAIDs may be useful in patients occasionally seen who have diarrhea that is unresponsive to other modalities.

Prostaglandins are released at the sites of inflammation, including the colonic mucosa in cases of active inflammatory bowel disease.[234-236] These eicosanoids potentially may affect colonic motility, epithelial cell proliferation, anion secretion and inflammation.[234-237] However, administration of prostaglandin inhibitors does not appear to reduce the inflammation.[238-240] Conversely, administering prostaglandins does not appear to be effective in maintaining remission in patients with ulcerative colitis.[241] Lipoxygenase products are also increased in patients with colitis,[242,243] and these products may be more important than prostaglandins in contributing to inflammation and electrolyte secretion.[244] Recent studies by Stenson and Lobos have suggested that inhibition of leukotrienes is the mechanism of action of sulfasalazine and presumably corticosteroids in this disease.[245] The role of leuko-

trienes in inflammatory bowel disease will likely be further defined with the development of specific lipoxygenase inhibitors.

The most extensive research on prostaglandins and the gastrointestinal tract has focused on the gastric and duodenal mucosa. Early observations that exogenous prostaglandins inhibited gastric acid secretion in animals[246] and in humans[247,248] suggested that prostaglandins could be therapeutic agents for treating peptic ulcer disease. Synthetic prostaglandin analogs—especially 15,15- and 16,16-dimethyl PGE_2—were more potent and longer acting than the natural prostaglandins. In studies using animals, exogenous prostaglandins were effective in healing duodenal ulcers and protecting against gastric mucosal injury induced by acid, alkali, base and a variety of other noxious stimuli.[226-228,249,250] These protective effects, however, were obtained with doses of prostaglandins less than 1/100th the dose needed to reduce acid secretion. The term "cytoprotection" is used to refer to this ability of exogenous prostaglandins to prevent damage to the gastric mucosa from noxious stimuli. Extensive research into the mechanism of cytoprotection has ensued. There are experimental data to support and to refute each of the proposed mechanisms: increased gastric mucosal blood flow, stimulation of cyclic AMP, prevention of gastric mucosal barrier disruption—that is, reducing hydrogen ion diffusion back into the mucosa—stimulation of mucus secretion, increase in alkaline secretion from nonparietal cells—that is, increasing the mucus-bicarbonate barrier—stimulation of cellular protein synthesis or transport or stabilization of lysosomes, maintenance of sulfhydryl compounds, increased cell proliferation and increase in mucosal surface hydrophobicity. It is clear from numerous clinical trials in humans that orally administered prostaglandins are equally effective as H_2 antagonists in healing duodenal ulcers, and prostaglandin analogs will likely be available for general clinical administration for this indication within a few years in this country. These compounds include 16,16-dimethyl PGE_2 (Upjohn), enprostil (Syntex), misoprostol (Searle), rioprostil (Ortho-Miles-Bayer) and trimoprostil (Hoffmann-La Roche).[251] These agents may also prove useful in treating gastric ulcer and hemorrhagic gastritis. The drugs are not without effects in other organs, and there is evidence that they may potentiate esophagitis associated with reduction in lower esophageal sphincter pressure.[252,253]

Endogenous production of prostaglandins from the gastric mucosa functions as a physiologic protective mechanism.[226-228,249,250] Current theory is that mild irritants, such as dilute ethanol, sodium chloride solutions and acid, stimulate prostaglandin production, which protects the gastric mucosa from subsequent necrotizing agents (more concentrated ethanol, for example). This phenomenon may also contribute to the therapeutic effects of sucralfate[254] and antacids.

Prostaglandins are likely involved in other aspects of gastrointestinal function. Gallbladder production of eicosanoids is increased in the inflamed tissues of cholecystitis and may contribute to decreased fluid absorption, gallbladder contraction and biliary pain.[255] Endogenous prostaglandins may also be involved in intestinal motility, although the clinical relevance to humans has not been shown. However, exogenous prostaglandins may be useful in stimulating motility in the treatment of postoperative ileus.[256]

Metabolic Disorders

There is laboratory and hypothetical evidence implicating prostaglandins in many metabolic processes including hormone secretion, neurotransmission and mineral and electrolyte disorders. The topics of glucose regulation and hypercalcemia of malignancy have received the most attention.

The role of arachidonic acid metabolites in glucose regulation has been controversial.[232,257-259] Prostaglandin E is synthesized by the pancreatic islet, and infusions of prostaglandin E in humans generally inhibit insulin secretion and increase circulating glucose concentration. Although aspirin immediately enhances insulin release in persons with type II diabetes mellitus, available data fail to substantiate a clinically significant glucose-lowering effect in prolonged trials. Indomethacin has the opposite effect of other NSAIDs, apparently by a non-cyclooxygenase-mediated mechanism. Recent data suggest that a lipoxygenase product, probably 12-HETE, produced by the islet cells may have a key role in mediating insulin release.[260]

Prostaglandins were first implicated as mediators of hypercalcemia of malignancy in animal models.[261] Presumably a prostaglandin metabolite released into the circulation stimulates bone resorption, and indomethacin normalizes the hypercalcemia.[261] Recent findings have challenged this interpretation.[262] In humans, as many as 20% of cancer patients with hypercalcemia have no apparent bone metastasis, implicating humoral mechanisms for the hypercalcemia. An early study by Seyberth and associates implicated excessive circulating PGE, presumably released from the tumors, as the cause of hypercalcemia in many of these patients.[263] Administering indomethacin or aspirin reduced the serum calcium levels in the patients who had increased PGE metabolite levels. Other investigators have also shown increased prostaglandins and reduced serum calcium levels with indomethacin in a few patients[264,265]; it is not established, however, that circulating prostaglandins exist in high enough concentration to directly induce bone resorption. There is also evidence that the tumors may have products that induce the bone to synthesize eicosanoids, which then cause release of calcium.[266] At this time, the topic remains unclear, and circulating prostaglandins are probably not the explanation for the hypercalcemia of malignancy.[267]

Arachidonic acid metabolites have been implicated in other aspects of cancer, including immunosuppression, cancer cell growth and metastasis, and there is a potential use for NSAIDs in combination with chemotherapy. Several recent review articles discuss these topics.[268-273]

Conclusions

Because of the recurring history of prostaglandin research in which many proposed physiologic functions could not be confirmed with subsequent better methods and study design, our concluding comment is to emphasize that readers carefully evaluate the assay techniques, the use of pharmacologic agonists and antagonists and the protocol design before accepting newly proposed physiologic functions for eicosanoids.

Research in arachidonic acid metabolites has increased greatly over the past two decades. The discovery of leukotrienes and related compounds will likely lead to clinical benefit in patients with asthma and inflammatory conditions. In

1985, prostaglandins have definitely become part of the clinical practice of medicine, particularly in the fields of reproduction, gastroenterology, nephrology and rheumatology.

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